LITHIUM: ANTIMANIC AND OFF-LABEL USES

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Topic Overview

Lithium is well-known as an antimanic agent and is administered for mood stabilization in patients diagnosed with bipolar disorder. More recently, lithium's use has been recognized off-label as an adjuvant treatment for conditions other than mania. An understanding of lithium treatment and monitoring requirements, as well as potential complications of treatment, is crucial to ensure patient awareness of symptoms and adherence. Clinicians who do not regularly prescribe lithium to treat bipolar disorder may be unfamiliar with all its uses, especially in special populations and for patients diagnosed with mixed mood states.

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How to Earn Credit: From August 29, 2022, through August 29, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
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Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Identify** monitoring requirements and recommended serum levels of lithium
2. **Describe** potential side effects and adverse reactions of lithium
3. **Compare** conditions for which lithium is prescribed, including off-label uses
4. **Identify** lithium toxicity

Disclosures

The following individuals were involved in the development of this activity: Amanda Mayer, PharmD, Susan DePasquale, MSN, PMHNP-BC, and Jeff Goldberg, PharmD, BCPP. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Lithium is a first-line choice for treating and preventing manic episodes in patients diagnosed with bipolar disorder. While it is generally accepted as a safe and effective drug for bipolar disorder, lithium has a narrow therapeutic window and requires close monitoring of laboratory trends of lithium levels and patient symptoms. A thorough understanding of the potential complications and adverse effects that could occur should be established prior to initiating lithium therapy. The following sections will discuss lithium's basic pharmacological profile and uses.

Lithium's Mechanism of Action

At the cellular level, lithium passes easily through sodium channels, and at high concentrations, it can block potassium channels. These actions by lithium allow it to compete with sodium, potassium, calcium, and magnesium ions.[1]

Lithium's mechanism of action on the central nervous system is unknown but there is evidence that lithium may interfere "with the synthesis, storage, release, and reuptake of monoamine neurotransmitters," thereby leading to its antimanic and antidepressant effects.[1] Lithium also enhances the uptake of tryptophan, promotes serotonin synthesis, and may also enhance the release of serotonin in the central nervous system. Lithium does not act as a sedative or depressant, and it does not cause euphoria.[1]

Lithium is rapidly absorbed after oral administration. The onset of its antimanic effect can be seen in 5 to 7 days. The full therapeutic effect of lithium usually takes 10 to 21 days.[1] The unabsorbed lithium is excreted unchanged in the urine.[2,3]

Lithium Treatment

Lithium is categorized as an antimanic and mood-stabilizing agent.[1-3] The goal of lithium therapy is to attain mood stabilization in patients who have

bipolar disorder. Lithium has a labeled indication as monotherapy for the treatment of patients with bipolar disorder. It may also be used off-label as an augmentation agent in the treatment of major depression.[1] There is also evidence that lithium can be useful in combination with other medications and for other off-label uses.

Bipolar Disorder

Lithium is currently indicated as a treatment for manic episodes and as a maintenance treatment in patients who have bipolar disorder.[1-3] Lithium can also be used off-label for bipolar depression as an adjunct with an antidepressant.[1-3] In patients experiencing a manic episode, lithium may be expected to produce a normalization of symptomatology within 1 to 3 weeks.[4]

Bipolar disorder is considered a chronic mental illness that is characterized by episodes of mania, hypomania, and major depression.[5] Bipolar disorder can be managed by medication treatment, but it cannot be cured. The mania, hypomania, and depression seen in bipolar disorder can be severe, with significant functional consequences that accompany a patient's mood episodes.[5]

The two subtypes of bipolar disorder are *type I* and *type II.* In bipolar disorder type I, manic, major depressive, and hypomanic episodes can be experienced.[5] In bipolar disorder type II, episodes can include hypomania and at least one episode of major depression. Lithium is the first-line treatment for manic episodes associated with bipolar I disorder.[5] For severe mania, lithium can be combined with antipsychotic medication, such as olanzapine, and/or another mood stabilizer, such as valproic acid, depending on the patient's history and prior response to treatment.[6]

Mild to moderate manic episodes can also be treated with lithium.[6,7] When used as maintenance treatment for bipolar disorder, lithium can lower the mania relapse rate. Long-term successful treatment with lithium may depend on genetic factors, as certain single nucleotide polymorphisms on

chromosome 21 have been shown to correspond with a good lithium response.[8]

Manic Episode: DSM-5 Criteria

Criteria A through D of the Diagnostic and Statistical Manual Fifth Edition (DSM-5) set forth the criteria to diagnose a manic episode. At least one, lifetime manic episode is required for the diagnosis of bipolar I disorder.[9] A manic episode is characterized by an abnormally and persistently elevated, expansive, or irritable mood and increased level of energy and activity lasting at least one week and for most of the day, nearly every day.[9]

A patient can be diagnosed as having a manic episode if the patient is observed with a mood disturbance and increased energy or activity, along with three or more of the symptoms (four symptoms if the mood is only irritable) listed below. The symptoms must exist to a significant degree representing a noticeable change in a patient's usual behavior:[9]

1. Grandiosity or inflated self-esteem
2. A reduced need for sleep
3. Hyperverbal or pressured speech
4. Flight of ideas or racing thoughts
5. Distractibility by patient report or observation
6. Increase in goal-directed activity (either socially, work or school, or sexually) or psychomotor agitation
7. Impulsivity or involvement in risky activities (excessive spending, business dealings, sexual behavior)

Patients with bipolar disorder can display a mood disturbance that is severe enough to cause significant impairment in social and/or occupational functioning and may require hospitalization to prevent harm to themselves or others. Mood disturbance can coincide with an episode of psychosis.[9] Symptoms of bipolar disorder may or may not be attributable to the physiological effects of substance use or another medical condition, so all other possible causes of the symptoms should be ruled out.[9]

Lithium and Circadian Rhythm

Bipolar disorder is known to be associated with altered circadian rhythm and insomnia. Research has focused on how lithium works at the cellular level to target the biological clock. Chronotypes may be divided into preferences: morning people who like to rise early or evening people who stay awake late.[10] During a study of 59 patients who responded well to lithium treatment, they found a "difference in chronotype, with higher levels of morningness," when compared to lithium non-responders.[10] Lithium responders tended to have a "short circadian period, a linear relationship between period and phase, and period shortening effects of lithium."[10] On the other hand, evening chronotype corresponded with a higher incidence of mood symptoms (depression, mania, and insomnia).[10] Individual variations in circadian rhythm in patients with bipolar disorder may impact lithium maintenance treatment and treatment outcomes.

As of 2019, sleep dysregulation reportedly affected an estimated 70% of patients with bipolar disorder and can persist even during euthymic periods.[11] Depressed and manic patients can experience changes in sleep onset, mixed insomnia/hypersomnia, an altered circadian phase, and can become preoccupied and anxious about their sleep patterns.[11] Prior studies have revealed that individuals with bipolar disorder had "a common pattern of eveningness preference."[11] with regards to a preference of wakefulness in the morning versus the evening.[11] Eveningness chronotypes associated with mood disorders were also associated with delayed circadian phase and delayed melatonin onset.[11] More studies are underway to explore the link between circadian rhythm, bipolar disorder, and the use of lithium.

Lithium and Aggression

The use of lithium to control symptoms of aggression in youth and adults has been studied. A Canadian review of lithium efficacy in aggressive youth with comorbid drug use and attention-deficit/hyperactivity disorder (ADHD) showed mixed outcomes.[12] One study showed no difference in behaviors in youth with co-occurring disorders who were prescribed lithium as compared

to placebo; however, other studies reported multiple improvements in behavioral outcomes. Data extracted from multiple studies suggested that lithium use was associated with a higher remission rate in aggressive youth than placebo.[12]

The presence of co-occurring conditions is common with bipolar disorder. These can include substance use, anxiety disorders, ADHD, personality disorders, and other conditions.[13] Comorbid psychiatric disorders can cover a range of psychopathology seen in individuals with bipolar disorder, which can make the treatment choice difficult. Lithium has also been compared with placebo in correctional settings, where patients showed chronic, impulsive, aggressive behavior that decreased significantly with the addition of lithium.[14]

Suicide Prevention Effect of Lithium

Suicide was among the top 9 leading causes of death in the United States in the year 2020.[15] Individuals with mood disorders have a 30-fold greater risk of suicide compared to patients without a mood disorder.[16] There is evidence that the long-term use of lithium may reduce the risk of suicide in patients with depression or bipolar disorder.[16]

Lewitzka, *et al.* (2015) provided a comprehensive review of studies that investigated the anti-suicidal effect of lithium. They found that the use of lithium for suicide prevention is uncommon; however, several studies were reviewed that confirmed lithium had an anti-suicidal effect on patients with affective disorders such as depression and bipolar disorder.[16] Observational studies included in the review by Lewitzka, *et al.*, showed that discontinuing lithium may increase the risk of suicide considerably.[16]

Little is known about the exact mechanism of action regarding lithium treatment and reduced suicide risk.[16] One of the mechanisms suggested is that lithium is a mood-stabilizing medication, which would lead patients with a good response to lithium to have less severe or frequent affective episodes. This may result in decreased suicidal behavior. The second suggested

mechanism is that lithium may decrease aggression and impulsivity, which could also lead to a reduction in suicidal behavior.[16]

Although there are many studies with evidence of lithium's anti-suicidal effects, there are noteworthy limitations to further studies of lithium's anti-suicidal effects. For example, suicide research is methodologically and ethically challenging, which limits the number of randomized controlled trials that can be done.[16] In addition, more studies are needed to determine a threshold or specific lithium level that may be required to induce anti-suicidal properties.[16] More research is needed to identify effective therapeutic strategies to decrease the risk of suicide.

Lithium and Clozapine-induced neutropenia or leukopenia

Clozapine is a second-generation antipsychotic mostly used for treatment-resistant schizophrenia.[17] Clozapine has the potential to cause the serious side effects of agranulocytosis and neutropenia. The incidence of agranulocytosis is approximately 1%, and the incidence of neutropenia is approximately 3%. White blood cell (WBC) and absolute neutrophil counts (ANC) must be monitored upon initiation and throughout the treatment of clozapine therapy. Patients are typically at the highest risk within the first 6 to 18 weeks of treatment with clozapine.[17]

There have been case reports of clozapine-induced neutropenia or leukopenia that were successfully reversed after lithium initiation.[17] Aydin, *et al.* (2016) presented a review of the literature with three case reports, all using once-daily dosing of lithium.[17] In all three case reports, patients saw normalization of WBC and ANC within 5 to 8 days and were able to maintain on clozapine and lithium combined therapy with no blood dyscrasias for 24 to 48 months. The authors reported no observed increase in serious adverse effects with the combination of lithium and clozapine; however, lithium levels should still be monitored to avoid lithium toxicity. The mechanism of lithium raising the WBC count is not completely understood, but it does present a good option in patients who are unresponsive to other antipsychotics and would benefit from clozapine.[17]

Dosing and Monitoring

The initial dose of lithium is typically 300 mg two or three times daily with a goal to reach a therapeutic dose that is often 900 mg to 1800 mg per day.[1] The serum lithium level to reach therapeutic effects is 0.8 to 1.2 mEq/L. Some patients may tolerate a serum level of 0.6 mEq/L better than 0.8 mEq/L and higher. Acute treatment often requires higher serum levels than maintenance treatment. Serum levels should be drawn 12 hours after the last oral dose and regularly until the patient is stabilized. In acute mania, the dose may be titrated by 300 mg every three days to the desired effect. Geriatric patients often respond to lower doses than younger adults and should be monitored closely for lithium toxicity.[1]

Lithium is typically dosed three times per day for immediate release and twice daily for extended-release formulations.[18] Newer studies, including one done by Singh, *et al. (2011),* have compared once-daily and twice-daily dosing of lithium.[18] Once daily dosing may help increase adherence and decrease adverse effects. These studies have shown that similar efficacy can be seen with once-daily and twice-daily dosing.[18] Dosing should be individualized based on clinical response and serum levels.

Lithium Side Effects and Adverse Outcomes

Patients that are prescribed lithium are routinely monitored for physical symptoms of toxicity and for elevated serum levels that could lead to serious adverse effects, such as renal impairment or thyroid dysfunction. There are considerable drug-drug interactions with the combined use of lithium and other drugs that require close monitoring to prevent a serious outcome.[1]

For adult patients with renal impairment and a CrCl of 30 to 89 mL/minute, therapy should be initiated at a lower dose and titrated slowly with frequent monitoring. In patients with a CrCl of < 30 mL/minute, the use of lithium should be avoided.[1]

Lithium is associated with nephrogenic diabetes insipidus, but the association between long-term lithium use and renal dysfunction has received mixed reviews.[19] Long-term lithium use can lead to deterioration in eGFR. Age, comorbidities, use of other nephrotoxic drugs, and history of lithium toxicity (lithium level > 0.80 mEq/L) have been associated with lower eGFR. In most patients prescribed long-term lithium, treatment is tolerated without precipitating renal dysfunction.[19]

The potential of renal dysfunction can occur at serum levels > 0.8 mEq/L, so cautious dosing should be considered in high-risk patients. Examples of patients at higher risk of lithium toxicity include the elderly and those taking medications known to increase lithium levels, such as nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, ACE inhibitors, *etc.*[19] Lithium levels should be monitored closely if any of these medications are deemed medically necessary while a patient is on lithium. As many of these interacting medications are usually initiated by a patient's primary care provider (as opposed to their psychiatric provider managing their lithium), pharmacists should be vigilant in communicating with all providers any time an interacting medication is prescribed to a patient taking lithium to avoid possibly exposing the patient to the toxic effects of lithium. Symptoms of acute lithium toxicity include nausea, vomiting, diarrhea, dysrhythmia, coarse tremor, muscle weakness, drowsiness, ataxia, and delirium.[1,19] Seizures, comas, and permanent neurological damage, such as dementia, can result from severe lithium toxicity. The risk of lithium toxicity is higher with sodium or volume depletion.[19]

Monitoring lithium levels and renal function are important when looking for signs of toxicity.[19] Long-term lithium use leads to a steady-state concentration in the brain and serum.[19] There are variations in serum lithium levels between individuals. In patients on chronically high doses of lithium, accumulations in central nervous system (CNS) tissue can lead to toxicity. If a patient failed to take a prescribed dose of lithium prior to a neurological toxicity test, the patient may have a normal serum level even though neurological toxicity is present.[19] Serum levels should be tested within 12

hours of taking the last dose of lithium to avoid a misinterpreted normal lithium level.[19]

Lithium can show diverse adverse effects on individuals. Those suspected to have lithium toxicity need to be treated with caution. In elderly patients on long-term lithium, a lithium level at the low end of the normal range should be the target goal.[19]

Case Study: Lithium Toxicity

The following case study focused on a 62-year-old male who had been diagnosed with bipolar disorder 25 years prior and currently has prostate cancer.[19] The patient had been stable on lithium with one documented stress-related hypomanic relapse. Symptoms of hypomania included high energy, insomnia, grandiosity, and irritability. The patient became highly elated, disinhibited, and disorganized while in the community prior to admission.[19] On admission to the hospital, he displayed pressured speech, flight of ideas, and appeared delusional. His adherence to medication was unknown. He was described as labile, tearful, laughing, anxious, pacing constantly, and making inappropriate, odd statements. He required an emergency hold and admission to the psychiatric unit.[19]

A medical history was obtained, and it was noted that he was diagnosed with low-risk prostate cancer with conservative treatment and monitoring.[19]. The patient had no documented allergies to medication. A bilateral fine tremor was noted, and Parkinson's disease was ruled out with an initial trial of selegiline. Treatment with propranolol was also attempted for essential tremor but discontinued due to lack of efficacy. Routine medications included: lithium 800 mg at bedtime, trazodone 50 mg at bedtime, and tadalafil 20 mg as needed.[19]

His family history was negative for mental illness. Social history and substance use showed that he lived in a shelter, was unemployed with documented disability due to bipolar disorder, and he denied using tobacco, alcohol, or illicit drugs.[19]

On physical examination, the patient's vital signs included a heart rate of 91 beats per minute, blood pressure of 135/79 mmHg, a temperature of 97.7 degrees Fahrenheit, and oxygen saturation of 96% on room air. The patient appeared malnourished, had bilateral tremors, and slurred speech. Laboratory testing showed the following:[19]

-Normal complete blood count (CBC)
-Normal liver function tests
-Normal thyroid-stimulating hormone
-Elevated creatinine of 1.39 mg/dL
-Elevated urea 60.66 mg/dL
-Slightly lowered estimated glomerular filtration rate (eGFR) of 52 mL/min
-The PSA was 6.82 µg/L, which was slightly raised but not clinically significant
-Serum lithium level was at the high end of the normal range at 0.95 mEq/L (> 12 hours after his last dose)
-Urinalysis and urine drug screens were negative

Initial treatment included rehydrating the patient with oral fluids. Lithium was initially stopped and replaced with olanzapine 10 mg at bedtime. Lithium was later restarted two weeks later due to worsening mania, and the coarse tremors reoccurred.[19] Chronic renal impairment and the reoccurrence of symptoms indicating toxicity led to the discontinuation of lithium. Sodium valproate was initiated as an alternative to lithium for bipolar disorder. The discontinuation of lithium corresponded with a vast improvement in tremors within two weeks. The authors believed that the patient developed chronic renal impairment during episodes of toxicity while taking lithium.[19]

After three months, the patient transitioned to a less restrictive level of care.[19] He continued to show poor insight and judgment, but overall, his mood and thoughts improved. He was less labile and showed gradual awareness of his mental illness. Olanzapine had been increased to 20 mg at bedtime; however, he developed rigidity and lip-smacking, both possible adverse effects of olanzapine. Procyclidine was utilized to help alleviate the adverse

effects of olanzapine, and sodium valproate was increased to 500 mg in the morning and 1000 mg at bedtime. There was no further deterioration of chronic kidney disease. He was eventually discharged to community mental health services on olanzapine and sodium valproate.[19]

Summary

Lithium is a first-line medication for the treatment of patients with bipolar disorder. It may also be used off-label as an augmentation agent in the treatment of major depression. Lithium's mechanism of action on the central nervous system is unknown but there is evidence that lithium may interfere "with the synthesis, storage, release, and reuptake of monoamine neurotransmitters," thereby leading to its antimanic and antidepressant effects. With careful prescribing and close monitoring, it can be used effectively and safely. Lithium should be used cautiously in patients with comorbid health conditions, especially impaired renal function. Patients should be counseled on lithium drug interactions and made aware of lithium toxicity symptoms. Close monitoring of neurological status and serum lithium level is essential in patients prescribed long-term lithium.

Course Test

1. **Lithium is an antimanic agent that acts as _____ in patients who have bipolar disorder.**

    a. a hallucinogen
    b. a mood stabilizer
    c. an antipsychotic
    d. an antidepressant

2. **For _____, lithium can be combined with an antipsychotic.**

    a. hypomania
    b. severe mania
    c. mild mania
    d. moderate mania

3. **Lithium has been shown to be effective in treating neutropenia caused by**

    a. lisinopril.
    b. clozapine.
    c. depakote.
    d. olanzapine.

4. **A patient with renal impairment and a CrCl of 30 to 89 mL/minute**

    a. may not take lithium.
    b. may take lithium without adjusting the dose since lithium does not affect renal function.
    c. may take lithium but with frequent monitoring.
    d. may take lithium but a high-sodium diet is recommended.

5. **True or False: Lithium has been shown to possibly reduce the risk of suicide in patients with an affective disorder, such as depression of bipolar disorder.**

    a. True
    b. False

6. **In patients on chronically high doses of lithium, accumulations in central nervous system (CNS) tissue can lead to**

    a. lithium toxicity.
    b. Brugada syndrome.
    c. hyperthyroidism.
    d. the development of thyroid auto-antibodies.

7. **A patient taking chronically high doses of lithium may have neurological toxicity but test normal because**

    a. the patient took the drug within 12 hours of being tested.
    b. the patient developed thyroid auto-antibodies.
    c. the patient failed to take a prescribed dose within 12 hours of being tested.
    d. the results were masked by the patient's high sodium diet.

8. **True or False: Lithium, in combination with other medication (such as antipsychotic medication), may benefit patients who are hostile, aggressive, or violent.**

    a. True
    b. False

9. **True or False: Lithium is not metabolized in the body and is excreted unchanged in the urine.**

    a. True
    b. False

10. **Which of the following medications are known to increase a patient's lithium levels?**

    a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
    b. ACE inhibitors
    c. Thiazide diuretics
    d. All of the above

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